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## **A cost-effectiveness analysis of trametinib plus dabrafenib as first-line therapy for metastatic BRAF V600-mutated melanoma in the Swiss setting**

Matter-Walstra, K ; Braun, R ; Kolb, C ; Ademi, Z ; Dummer, R ; Pestalozzi, B C ; Schwenkglenks, M

**Abstract:** Background: The treatment of patients with metastatic melanomas that harbour BRAF V600E or V600K mutations with trametinib plus dabrafenib appears to be superior to treatment with vemurafenib alone. This treatment regimen is likely to become available in Switzerland in the near future. Objectives: To determine the cost-effectiveness of trametinib plus dabrafenib. Methods: A Markov cohort simulation was conducted to model the clinical course of typical patients with metastatic melanoma. Information on response rates, clinical condition and follow-up treatments were derived and transition probabilities estimated based on the results of a clinical trial that compared treatment with trametinib plus dabrafenib vs. vemurafenib alone. Results: Treatment with trametinib plus dabrafenib was estimated to cost an additional CHF199 647 (Swiss francs) on average and yield a gain of 0.52 quality-adjusted life years (QALYs), resulting in an incremental cost-effectiveness ratio of CHF385 603 per QALY. Probabilistic sensitivity analyses showed that a willingness-to-pay threshold of CHF100 000 per QALY would not be reached at the current US price of trametinib. Conclusions: The introduction of trametinib in Switzerland at US market prices for the treatment of metastatic BRAF V600-mutated melanoma with trametinib plus dabrafenib is unlikely to be cost-effective compared with vemurafenib monotherapy. A reduction in the total price of the combination therapy is required to achieve an acceptable cost-effectiveness ratio for this clinically promising treatment.

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## **A cost-effectiveness analysis of trametinib plus dabrafenib as first-line therapy for metastatic *BRAF* V600-positive melanoma in the Swiss setting**

**Running head:** Cost-effectiveness of trametinib plus dabrafenib for melanoma

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### **What is known about this topic?**

- Several new promising treatments for patients with metastatic melanoma that harbour *BRAF* V600E or V600K mutations have recently become available
- Trametinib is not yet available in Switzerland, but approval is expected in 2015
- These new treatments are very expensive

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### What does this study add?

- Although clinically promising, at current US trametinib prices, trametinib plus dabrafenib will not be cost effective compared to vemurafenib in the Swiss setting
- Only a reduction in the price of the combination therapy would make this therapy cost effective

### Abstract

**Background and Objective:** The treatment of patients with metastatic melanomas that harbour *BRAF* V600E or V600K mutations with trametinib plus dabrafenib appears to be superior to treatment with vemurafenib alone. This treatment regimen is likely to become available in Switzerland in the near future. However, its cost-effectiveness is unknown.

**Methods:** A Markov cohort simulation was conducted to model the clinical course of typical patients with metastatic melanoma. Information on response rates, clinical condition, and follow-up treatments were derived and transition probabilities estimated based on the results of a clinical trial that compared treatment with trametinib plus dabrafenib versus vemurafenib alone.

**Results:** Treatment with trametinib plus dabrafenib was estimated to cost an additional CHF199,647 on average and yield a gain of 0.52 quality-adjusted life years (QALYs), resulting in an incremental cost-effectiveness ratio of CHF385,603/QALY. Probabilistic sensitivity analyses showed that a willingness to pay threshold of CHF100,000/QALY would not be reached at trametinib's current United States price.

**Conclusion:** The introduction of trametinib in Switzerland at US market prices for the treatment of metastatic *BRAF* V600-positive melanoma with trametinib plus dabrafenib is unlikely to be cost effective compared to vemurafenib monotherapy. A reduction in the total price of the combination therapy is required to achieve an acceptable cost-effectiveness ratio for this clinically promising treatment.

## Introduction

At 25.8 per 100,000 population per year, melanoma incidence in Switzerland is the highest of 40 European countries, and Switzerland is ranked sixth in Europe in terms of melanoma mortality (3.5 per 100,000) <sup>1</sup>. Approximately 50% of melanomas harbour activating *BRAF* mutations <sup>2</sup>, and drugs that inhibit the downstream mitogen-activated protein kinase (MAPK) cascade in melanoma cells have been developed over the last few years. These targeted therapies have had substantial clinical impact in patients with *BRAF* mutated melanoma. The MAPK-targeting therapies include several selective tyrosine kinase inhibitors such as vemurafenib (VEM), dabrafenib (DAB), and the MEK1 and/or MEK2 enzyme inhibitors trametinib (TRAM) <sup>2-8</sup>, binimetinib<sup>9</sup> or cobimetinib<sup>10</sup>. These drugs have all been shown to improve clinical response rates (alone or in combination) , progression-free survival (PFS) and overall survival (OS)<sup>11, 12</sup> in patients with metastatic *BRAF*-mutated melanomas when compared to drugs such as dacarbazine<sup>4</sup>, and other chemotherapies <sup>13</sup>. The reported median progression free survival times for these new drugs (in mono-therapy) are quite similar. All of these targeted therapies are now available in Switzerland except for trametinib<sup>14</sup>. However, these new drugs are extremely expensive compared to standard chemotherapies.

In a recent randomised controlled trial, trametinib plus dabrafenib (TRAM+DAB) combination therapy was compared to VEM monotherapy <sup>12</sup>. In previously untreated patients with metastatic melanomas harbouring *BRAF* V600E or V600K mutations, TRAM+DAB (median PFS 11.4 months, median OS not reached) significantly improved progression free and overall survival compared to VEM monotherapy (PFS 7.3 months, OS 17.2 month). Overall toxicity was not increased.

A cost-effectiveness analysis from the Canadian healthcare perspective showed that treatment with TRAM alone vs. dacarbazine may not be cost effective from the societal perspective but may be cost-effective compared to VEM <sup>15</sup>. In addition, DAB has been shown not to be cost-effective compared to dacarbazine in the Canadian healthcare system <sup>16</sup>. Curl et al <sup>17</sup> showed that VEM itself would not be cost effective with its current price compared to dacarbazine in the US. VEM in combination with

ipilimumab compared to dacarbazine was more cost-effective but the incremental cost effectiveness ratio (ICER) was still higher than most desirable willingness to pay thresholds.

DAB and VEM have both been approved for use in Switzerland, and their costs are known ([www.swissmedic.ch](http://www.swissmedic.ch), <http://compendium.ch>). VEM can be regarded as one of the standard therapies for the given indication in Switzerland. However, reimbursement is conditional upon pre-approval by the responsible health insurance company<sup>18</sup>. TRAM so far is not yet available in Switzerland. If TRAM is approved in Switzerland (expected in 2015) for *BRAF*-positive metastatic melanoma patients and used in clinical practice in combination with DAB rather than VEM, it is important to determine its cost-effectiveness prior to approval to help negotiate optimal prices for healthcare acquisition.

Therefore, we used the clinical outcomes reported by Robert *et al.*<sup>12</sup> to evaluate the cost effectiveness of the TRAM+DAM strategy compared to VEM with respect to the Swiss healthcare system. The USA price for TRAM was used for the base case evaluation, and different pricing scenarios for the combination therapy were investigated for the assessment of possible willingness-to-pay (WTP) thresholds.

## Methods

A Markov model was constructed to assess the cost-effectiveness of treatment strategies for patients with metastatic *BRAF* V600-mutated melanoma. Combination therapy with dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) was compared to vemurafenib (960 mg twice daily) orally as first-line therapy. The clinical model was based on the study by Robert *et al.*<sup>12</sup>. Drug therapies, major adverse events, and second-line treatments during progression were considered as direct medical costs from the perspective of the Swiss healthcare system, and a lifelong time horizon was adopted to capture related costs and outcomes. Drug prices were based on Swiss prices and tariff lists (except for TRAM, which was based on USA prices and converted to Swiss Francs according to the average exchange rate in January 2015). The health state utilities used in the model were obtained from the

literature<sup>15, 19</sup>. The effect of discounting for cost and effects on the ICER for a discount rate of 3 and 6% per year after the first year was assessed.

Metastatic melanoma patients eligible for the original multicentre, open-label phase 3 study had proven *BRAF* V600E or V600K mutations. In total, 704 patients were randomised to receive either TRAM (2mg/day)+DAB (150mg/twice daily) or VEM (960mg/twice daily) orally until progression; some patients continued on the study medication for some time after disease progression<sup>12</sup>. Of the observed adverse events, 48% (TRAB+DAB arm) and 57% (VEM arm) were grade 3. According to a personal communication with Prof. R. P. Braun, University Hospital Zürich, almost none of the observed events reported would have required any specific cost-inducing treatments except for the treatment of cutaneous squamous cell carcinoma, which was observed in VEM-treated patients more often (grade 3, 17%) than TRAM+DAB-treated patients (grade 3, 1%).

In our analysis, the primary endpoint was the incremental cost-effectiveness ratio (ICER) expressed as cost per quality-adjusted life year (QALY) gained of TRAM+DAB compared to VEM in patients with metastatic *BRAF*-mutated melanoma. ICERs were compared to possible WTP thresholds of CHF50,000-CHF100,000 per QALY gained.

In addition, one-way, two-way, and probabilistic sensitivity analyses were performed to test the robustness of the results. Sensitivity analyses for the given TRAM+DAB drug prices and one alternative price scenario were carried out to evaluate the price at which TRAM combined with DAB may be cost effective. Furthermore, the budget impact on the Swiss healthcare system was estimated. The model was built and all analyses were performed in TreeAge Pro 2015®.

#### *Model structure*

The Markov model comprised three mutually exclusive health states as shown in Figure 1: stable/responsive (progression-free) disease, disease progression, and death. A cycle length of one month was chosen to match the outcomes and medication schemes of the original study. All patients

started with stable progression-free disease, where they either remained or transitioned to progressive disease. Once in the progressive stage, patients could remain in this stage or transition to death.

#### *Clinical effectiveness and quality of life*

Effectiveness data were inferred from the PFS and overall survival outcomes reported in the original publication. Hazards were assumed to be constant over time, and the median time spent in each state was used to estimate hazard rates for the VEM strategy based on the formula: hazard rate =  $-\ln(0.5)/\text{median time in state}$ . Thereafter, hazard rates were converted into Markov state transition probabilities. To model time to progression and overall survival in the TRAM+DAB strategy, hazard rates in the VEM strategy were multiplied by the applicable hazard ratios (HR).

The median time from progression to death in the VEM strategy was estimated to fit the reported median overall survival time in the VEM strategy because this information was not provided in the original publication. Thereafter the HR for death was used to estimate an approximate median overall survival time for the TRAM+DAB strategy, which was not available at the time of publication.

Quality-adjusted progression-free time and time in progression were calculated according to published utilities: VEM calculations were based on a population-based survey using the standard gamble method<sup>17, 19</sup>, and for TRAM+DAB (using utilities for TRAM as reported by Amdahl et al.<sup>15</sup>) calculations were EQ-5D based (see <http://www.euroqol.org>)<sup>15, 20</sup>.

All values for the base case input parameters are listed in table 2 (mean values).

#### *Use of medical resources and unit costs*

Only drug use and adverse event information were provided in the publication by Robert *et al.*<sup>12</sup>; there were no data on other medical resource use such as hospitalisations or other supportive care. Therefore, the costs considered in the model were only based on study and follow-up drug costs (see

Table 1 for unit prices and treatment schemes) and estimated costs for the treatment of adverse events. A price of CHF165/mg of TRAM was assumed, and the prices for the other drugs were set according to Swiss tariffs. No costs for in- and/or out-patient supportive care were included (see details in the discussion).

No costs were attached to specific adverse events; instead, an overall cost distribution from a minimum of CHF0 (for adverse events not requiring treatment) to a maximum of CHF 1,400 per adverse event was employed to cover possible treatment costs in both strategies. Costs for the treatment of cutaneous squamous cell carcinoma were estimated to be  $\pm$ CHF1,000 and were included in the distribution.

Follow-up treatments were implemented in the model as observed in the original study (Supplementary Material <sup>12</sup>, Table 1). Swiss public healthcare prices were used for all drugs except TRAM (USA price, no Swiss price available). The duration of follow-up treatments with study medication was modelled according to the original study. Three follow-up cycles of drugs other than the study medications were assumed, as per common practice.

#### *Sensitivity analyses and price scenarios*

The influence of uncertainty on key model parameters was assessed by a series of one-way sensitivity analyses and a probabilistic sensitivity analysis. In the one-way sensitivity analyses, all parameters subject to uncertainty were varied across plausible ranges as shown in Table 2.

Probabilistic sensitivity analysis (a second-order Monte Carlo simulation) was based on the corresponding distributions of the parameters (see Table 2).

A two-way sensitivity analysis, in which the price of TRAM and DAB was varied simultaneously, was performed in order to calculate alternative ICERs for comparison with possible WTP thresholds of CHF50,000 and CHF100,000 per QALY. Although there is no official cost per QALY gained threshold in Switzerland, WTP thresholds including a WTP threshold of CHF 80,000 per QALY were used in line with a recently published analysis for the Swiss setting <sup>21</sup>. In addition, two separate probabilistic



sensitivity analyses were performed: one with base case prices for TRAM+DAB and one with both drugs half the price of the base case situation. These analyses provided information about the probability of the TRAM+DAB treatment being cost effective compared to the given WTP thresholds.

#### *Model validation*

The model was adjusted to match the progression-free and overall survival data (only for the VEM treatment strategy) in the original Robert *et al.*<sup>12</sup> study. Trackers for progression-free survival and overall survival were included to assess for correct data fit. All outputs were reviewed for plausibility. Key input parameters were subjected to extreme variation to assess the accuracy of the model.

#### **Results**

The clinical outcomes of the original study were reproduced in the model as follows: median PFS for TRAM+DAB and VEM in the Robert *et al.*<sup>12</sup> study were 11.4 and 7.3 months, respectively. The model-based median PFS was 11.3 months (TRAM+DAB) and 7.4 months (VEM), thereby satisfactorily matching the results of the original study. The model-based median overall survival for the VEM arm also reasonably fitted the original data (17.8 in the model versus 17.2 months in the original data). With respect to the TRAM+DAB strategy, the median overall survival from the model was 25.9 months. This result could not be directly confirmed using the original data (no median overall survival reached at the time point of data extraction for publication<sup>12</sup>) but seemed plausible from extrapolation of the original data.

The base case model indicated that TRAM+DAB (mean cost CHF311,421; mean effect 1.54 QALYs) compared to VEM (mean cost CHF111,773; mean effect 1.02 QALYs) in patients with *BRAF*-positive metastatic melanoma leads to a gain of 0.52 QALYs per patient at an additional cost of CHF199,647. This resulted in an ICER of CHF385,603 per QALY gained (see Table 3). Discounting by 3 or 6% per

year (starting after the first year) for costs and effects marginally increased the ICER as shown in Table 3.

Univariate sensitivity analyses showed that varying the utility (quality of life) for the time in progression for the TRAM+DAB strategy had the highest impact on the ICER, followed by the HR for death. Further parameters that had a substantial impact were utility PFS for the TRAM+DAB strategy, hazard ratio PFS, time to PFS (VEM), time from PFS to death (VEM), and the utilities for the corresponding VEM stages, as shown in Figure 2. None of the tested variations in key parameters resulted in an ICER below a WTP threshold of CHF100,000/QALY. In a separate analysis, we applied the utility for the progressive disease state observed in VEM-treated patients to both strategies. The ICER increased to 508'532CHF/QALY. Using the utility for the progressive disease state applied in TRAM+DAB patients for both strategies resulted in a similar ICER of 502'397CHF per QALY gained. In both cases the ICER increased because the differences in effects decreased.

Two-way sensitivity analysis (Figure 3), in which the prices of TRAM and DAB were varied simultaneously, showed that TRAM would need to be priced at almost zero with the current price of DAB in order to achieve an ICER of no less than CHF100,000/QALY. Even if the price of DAB could be reduced by at least 50%, the price of TRAM would need to be far below the current US price in order to achieve ICERs that might be regarded as acceptable.

Probabilistic sensitivity analyses confirmed these results (Figure 4). Based on current prices, the probability that TRAM+DAB versus VEM would be cost effective was zero. Reducing both the price of TRAM and DAB by 50% resulted in a 3% probability that the TRAM+DAB treatment compared to VEM would be cost-effective with respect to a WTP threshold of CHF50,000/QALY and 73% with respect to a WTP threshold of CHF100,000/QALY. A combined price for TRAM+DAB of about CHF 5'335 per month would match a WTP of CHF 50'000 per QALY gained; a price of about CHF 7'590 would match a WTP of CHF 100'000 per QALY. We next estimated the impact of the introduction of TRAM+DAB combination therapy on the Swiss healthcare system budget. Based on 2012 data, mortality from melanoma in Switzerland was 3.65/100,000<sup>1</sup>, i.e., approximately 300 melanoma deaths per year in a

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population of 8,039,100 (2012, www.bfs.admin.ch). If 40% of the patients' cancers have a suitable *BRAF* mutation and assuming all are treated with TRAM+DAB, this would result in a total average spend of 37 million Swiss francs (drug costs only), almost 24 million more than treatment with VEM.

## Discussion

The global incidence of melanoma is rapidly increasing in the white population<sup>22</sup>. The development of diagnostic tests that detect specific mutations to direct targeted therapy has resulted in several new treatment options with promising clinical outcomes<sup>4-8, 12, 13</sup>. However, the costs of these new treatments are high, and several health economic analyses have concluded that they might not be cost effective<sup>15-17</sup>. In our study, we analysed the cost-effectiveness of trametinib (TRAM) plus dabrafenib (DAB) combination therapy versus vemurafenib (VEM) for patients with *BRAF* V600-mutated metastatic melanoma. Follow up treatments were modelled as observed in the clinical trial performed by Robert *et al.*<sup>12</sup>. VEM is frequently used in Switzerland despite its high costs, and lack of cost-effectiveness reported for the US<sup>17</sup>. TRAM is expected to be approved for use in Switzerland in 2015 (personal communication Prof. Dummer), but the drug price for the Swiss market has yet to be established.

Using clinical data from the study performed by Robert *et al.*<sup>12</sup>, treatment with TRAM+DAB compared to VEM resulted in a predicted ICER of CHF385,603 per QALY gained and discounting costs and effects for 3 or 6% slightly increased the ICER. This is in line with other cost-effectiveness analyses for TRAM<sup>15</sup> and other treatment strategies for *BRAF*-mutated metastatic melanoma<sup>17</sup>. This ICER is far higher than the WTP thresholds proposed - but not generally accepted - for Switzerland (CHF80,000/QALY<sup>21</sup>) and those used in other European countries (between 30,000 and 50,000 €/QALY<sup>23-25</sup>). Since the Swiss market price for TRAM is still unknown, we evaluated possible price scenarios for TRAM that would meet acceptable WTP thresholds: we calculated that the price of TRAM would need to be almost zero in order to make this combination therapy cost effective, which

is, quite clearly, unrealistic. The probability that combination therapy might become cost effective only increases if the total “combination therapy” price can be reduced (cost reduction for DAB and a far lower price for TRAM than currently set in the USA). Moreover, since the cost-effectiveness of vemurafenib compared to other treatments is not given<sup>17</sup>, the probability that TRAM+DAB combination therapy is cost effective compared to these (older) therapies is highly unlikely. Although there is no official WTP threshold for Switzerland, these analyses show that introducing TRAM to the Swiss market for metastatic melanoma may be of high clinical benefit but is highly unlikely to be cost-effective.

The impact of an additional 24 million Swiss Francs spend (compared to treatment with VEM) would increase the cancer treatment budget in Switzerland by 0.5% (the total treatment costs for cancer patients in Switzerland in 2011 was 4,005 million Swiss Francs), or 5% when only drug costs are taken into account ([www.interpharma.ch](http://www.interpharma.ch)). This would only have a marginal impact compared to overall treatment costs for cancer patients in Switzerland, mostly due to a low number of eligible patients per year.

Our analysis has several limitations. First of all, at the time point of analysis as reported in the underlying trial by Robert *et al.*<sup>12</sup> medium OS in the TRAM+DAB arm was not yet reached. Possibly durable responses in some patients would not have been visible yet. The occurrence of such long-term responses could decrease the ICER, but there are no data so far to affirm this possibility. . Then we could only examine the cost data for drug treatments since no clinical care data (hospitalisations, supportive or palliative care) were available. However, it can be assumed that clinical care is similar for all patients; only the duration of care due to different overall survival times between treatment strategies might have produced a cost difference. It is unclear how strong these cost effects might be on the ICER, but given the longer overall survival time for patients in the TRAM+DAB strategy, these patients could reasonably be assumed to incur higher costs and further disadvantage this treatment option. Furthermore, quality of life data were not recorded in the original study, and we had to rely on health state utility information from other studies for modelling, using different methodologies<sup>15</sup>,

Accepted Article

<sup>19</sup>. The utilities used for the TRAM+DAB strategy were those used for patients treated with TRAM monotherapy, and it is unclear if the combination therapy might have resulted in other utilities. As shown in the univariate sensitivity analyses, variation of utility parameters had a strong effect on the ICER and, depending on the shift in estimated utilities for the combination therapy, this may affect the ICER. Moreover, the model did not include a separate state representing “response to therapy” with a possibly reduced disease burden and thus higher utility than other persons in the progression free state. In addition, we assumed that the cost for treating the observed adverse events would not be very high (personal communication, R. Braun). This contradicts the results from an other study, which concluded that the incremental costs associated with many melanoma treatment-related adverse events are substantial <sup>26</sup>. However, this previous study included patients treated with paclitaxel, vemurafenib, ipilimumab, dacarbazine, temozolomide, high-dose interleukin 2, interferon  $\alpha$ , dabrafenib, or trametinib, each of which have very different safety implications. These results are therefore not directly comparable and underpinned our decision to not add additional cost uncertainty into the model by costing separate adverse events without proof of validity. Finally, patients in usual clinical practice may not be as fit as the study population and might be less likely to benefit from these antineoplastic treatments, further impairing the cost-effectiveness of TRAM+DAB.

## Conclusion

Here, we show that the introduction of trametinib, priced according to its current US market cost, to treat Swiss metastatic *BRAF* V600-positive melanoma patients with a combination therapy of trametinib and dabrafenib is unlikely to be cost effective compared to vemurafenib monotherapy.

The total price for the combination therapy needs to be reduced by negotiating lower prices for both trametinib and dabrafenib to achieve an acceptable cost-effectiveness ratio for this clinically promising treatment.

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## Figure legends

**Figure 1.** Model structure.

**Figure 2.** One-way sensitivity analysis for the 12 input parameters with the largest effect on the ICER.

Legend: Based on 2.5% and 97.5% percentiles as shown in Table 2. Results shown are for 0% discounting, DAB=dabrafenib, FU=follow up, HR=hazard ratio, PFS=progression free survival, TRAM=trametinib, VEM= vemurafenib

**Figure 3.** Two-way sensitivity analysis for the effect of the costs of trametinib and dabrafenib on the ICER.

Legend: Results shown are for 0% discounting

**Figure 4.** Probabilistic sensitivity analysis for the base case trametinib and dabrafenib prices and for a 50% reduction in price.

Legend: For a price reduction of trametinib and dabrafenib of 50%: willingness to pay = 50,000, probability cost effective = 3%; willingness to pay = 100,000, probability cost effective = 73%. Results shown are for 0% discounting

## Tables

**Table 1.** Unit prices and treatment schedules for cost input parameters

Treatment	Unit price	Dose	Schedule	Source
Dabrafenib	1.15 CHF/mg	300mg	daily	<a href="http://compendium.ch/search/all/dabrafenib/startwith/de">http://compendium.ch/search/all/dabrafenib/startwith/de</a>
Trametinib	165 CHF/mg	2mg	daily	price based on US\$ see <a href="http://GoodRx.com">http://GoodRx.com</a>
Vemurafenib	0.2 CHF/mg	960mg	twice daily	<a href="http://compendium.ch/search/all/vemurafenib/startwith/de">http://compendium.ch/search/all/vemurafenib/startwith/de</a>
Ipilimumab*	98 CHF/mg	3mg/kg*	once in 3 weeks	<a href="http://www.compendium.ch/search/all/ipilimumab/startwith/de">http://www.compendium.ch/search/all/ipilimumab/startwith/de</a>
Dacarbazine*	0.61 CHF/mg	850mg/m <sup>2</sup> #	once in 3 weeks	<a href="http://www.compendium.ch/search/full/dacin/contains/de">http://www.compendium.ch/search/full/dacin/contains/de</a>
Intravenous application	375 CHF/application			<a href="http://www.tarmedsuisse.ch/">http://www.tarmedsuisse.ch/</a>
Other FU Therapies	CHF 141-9971/cycle			<a href="http://compendium.ch/">http://compendium.ch/</a>
Costs for adverse events	CHF 0-1400/adverse event			

\* = intravenous application, ° basis = 60kg, # basis = 60kg / 174 cm

**Table 2.** Distribution type and input values for the sensitivity analyses

Treatment arm	Type	Variable	Distribution type used in probabilistic sensitivity analysis	Mean°	Median°	2.5th percentile°	97.5th percentile°
	Costs	Costs for adverse events	Gamma <sup>1)</sup>	93	41	0.08	562
		Costs for other FU treatments per cycle	From List*	5098	5019	161(min)	9918(max)
	Outcome <sup>12</sup>	Hazard ratio death	Lognormal <sup>2)</sup>	0.69	0.69	0.55	0.89
		Hazard ratio progression free survival	Lognormal <sup>2)</sup>	0.56	0.56	0.44	0.69
DAB + TRAM	Outcome <sup>12</sup>	% adverse events grade 3	Beta <sup>4)</sup>	48%	48%	43%	53%
	Treatment <sup>12</sup>	% patients continuing study treatment in FU	Beta <sup>4)</sup>	23%	23%	20%	26%
		% patients with dose reduction DAB+TRAM	Beta <sup>4)</sup>	33%	33%	28%	38%
		% patients with dacarbazine in FU	Beta <sup>4)</sup>	3%	3%	2%	5%
		% patients with ipilimumab in FU	Beta <sup>4)</sup>	12%	12%	9%	15%
		% patients with other treatments in FU	Beta <sup>4)</sup>	4%	4%	2%	7%
		% patients with VEM in FU	Beta <sup>4)</sup>	5%	5%	3%	8%
		Duration of study medication (month) in FU	Gamma <sup>2)</sup>	2.47	1.56	0.04	9.14
	Utility <sup>15</sup>	Utility progression free survival	Beta <sup>3)</sup>	0.78	0.78	0.73	0.83
		Utility progression	Beta	0.72	0.72	0.56	0.87
VEM	Outcome <sup>12</sup>	% adverse events grade 3	Beta <sup>3)</sup>	57%	57%	52%	62%
		Time to progression in months	Gamma <sup>2)</sup>	7.34	7.30	4.37	11.04
		Time from progression to death in months	Gamma <sup>2)</sup>	4.63	4.54	2.61	7.03



	Treatment <sup>12</sup>	% patients continuing study treatment in FU	Beta <sup>4)</sup>	23%	23%	19%	28%
		% patients with dose reduction VEM	Beta <sup>4)</sup>	39%	39%	33%	44%
		% patients with DAB in FU	Beta <sup>4)</sup>	8%	8%	5%	11%
		% patients with dacarbazine in FU	Beta <sup>4)</sup>	8%	8%	6%	11%
		% patients with ipilimumab in FU	Beta <sup>4)</sup>	22%	22%	18%	27%
		% patients with other treatments in FU	Beta <sup>4)</sup>	11%	11%	8%	15%
		Duration of study medication (months) in FU	Gamma <sup>2)</sup>	1.45	1.03	0.06	5.54
	Utility <sup>19</sup>	Utility progression free survival	Beta <sup>3)</sup>	0.80	0.80	0.78	0.82
		Utility progression	Beta <sup>3)</sup>	0.52	0.52	0.48	0.56

\* Swiss pharmaceutical drug information: <http://compendium.ch/>, <sup>1)</sup> results as calculated for 1000 samples of the distribution, <sup>2)</sup> representing base case +/- 50%, <sup>3)</sup> based on 95% confidence interval, <sup>4)</sup> estimated from mean and standard error, <sup>4)</sup> based on observed frequencies in the trial by Robert et al.<sup>12</sup>

**Table 3.** Base case results

Discounting	Strategy	Cost CHF	Effect in Life Years	Effect in Utilities	Effect in QALYs	ICER CHF/QALY
0%	VEM	111,773	1.49	0.685	1.02	385,603
	DAB+TRAM	311,421	2.02	0.762	1.54	
	Difference DAB+TRAM and VEM	199,647	0.53	0.078	0.52	
3%	VEM	110,187	1.46	0.685	1	395,204
	DAB+TRAM	302,747	1.95	0.764	1.49	
	Difference DAB+TRAM and VEM	192,560	0.49	0.079	0.49	
6%	VEM	108,730	1.43	0.692	0.99	404,542
	DAB+TRAM	294,984	1.89	0.767	1.45	
	Difference DAB+TRAM and VEM	186,255	0.46	0.075	0.46	



